VI. Study designs

- It is part of any type of studies.
- It is critical to the success of a study.
- The success relies on the best knowledge of epidemiology and is closely to the statistical analysis to be carried out.

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Types I and II errors

Decisions in hypothesis testing

Decision	H_0 is true	H_0 is false
Not reject H_0	no error	type II error
Reject H_0	type I error	no error

- α=P(type I error)=P(reject H_0 when H_0 is true)
- β=P(type II error)=P(accept H_0 when H_0 is false)
- Type I error is directly set by the analyst
- Type II error depends on the sample size

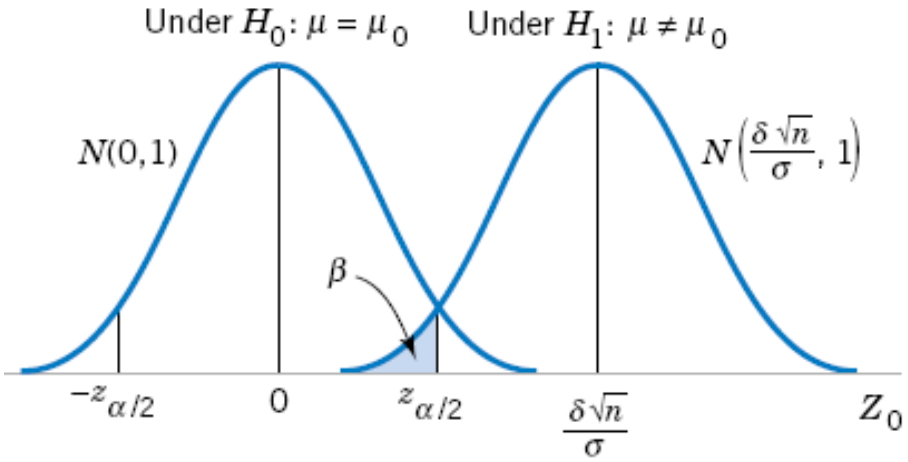
A two-sided test of a normal mean

- For a two-sided hypothesis and the true value of mean is $\mu=\mu_0+\delta$

$$H_0: \mu = \mu_0$$
$$H_1: \mu \neq \mu_0$$

$$Z_0 = \frac{\overline{X} - \mu_0}{\sigma/\sqrt{n}} = \frac{\overline{X} - (\mu_0 + \delta)}{\sigma/\sqrt{n}} + \frac{\delta\sqrt{n}}{\sigma}$$

$$Z_0 \sim N\left(\frac{\delta\sqrt{n}}{\sigma}, 1\right)$$



$$\beta \simeq \Phi\left(z_{\alpha/2} - \frac{\delta\sqrt{n}}{\sigma}\right)$$

$$-z_\beta \simeq z_{\alpha/2} - \frac{\delta\sqrt{n}}{\sigma}$$

$$n \simeq \frac{(z_{\alpha/2} + z_\beta)^2 \sigma^2}{\delta^2}$$

Some facts of chi-squared distribution

- Let X_i~ i.i.d. N(μ_i,1), i=1,…,v, then Y=Σx_i^2 has noncentral chi-squared distribution with characteristic function

$$\phi(t) = \exp[(it\delta)/(1-2it)]/[(1-2it)^{\nu/2}]$$

- where $\delta=\Sigma\mu_i^2$ and therefore E(Y)=v+δ, V(Y)=2v+4δ
- Power of a chi-squared statistic given significance level α can be obtained as

$$\int_{\chi_{\alpha(\nu,0)}}^{\infty} d\chi^2(\nu,\delta)$$

- where $\chi^2_{\alpha(\nu,0)}$ is the 100(1-α) percentage point of the central chi-squared with v degree(s) of freedom and the δ is the noncentrality parameter.

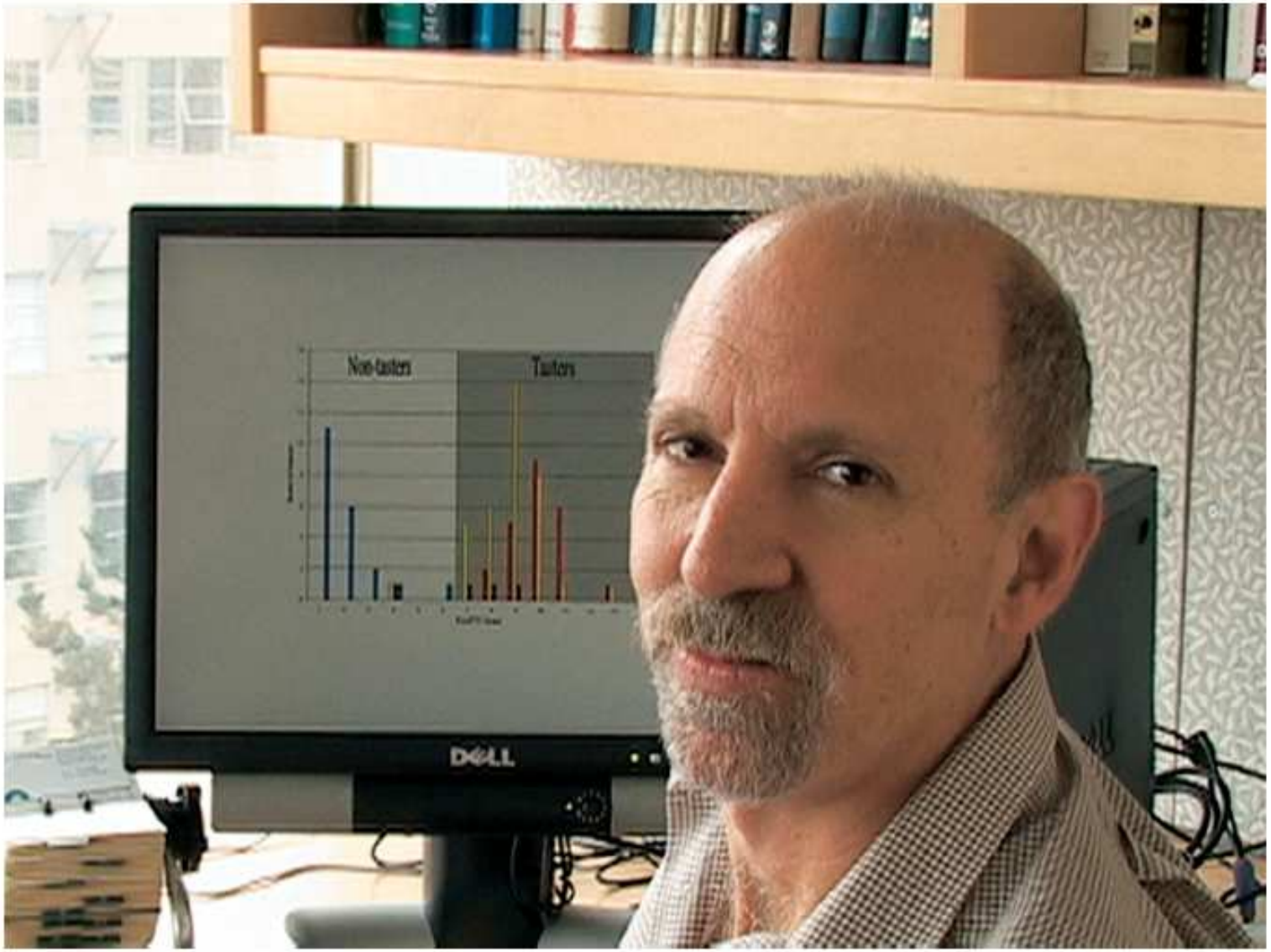
Linkage study

- Parametric linkage method can be done with SLINK/FastSLINK as describe earlier.
- DESPAIR is included as part of SAGE, designed for whole autosomal genome screening using affected pairs of relatives of a particular type or discordant relative pairs into the study. The program can be used to determine, for specified power and significance level, the optimal two-stage study design – i.e., how many pairs of relatives should be studied, how many equally spaced markers should be used initially, and what criterion should be used to specify the markers around which further searching should be done. Alternatively, the program will calculate either the number of relative pairs required for a given number of first-stage markers, or the number of markers required for a given number of relative pairs.
- It is nevertheless only available from http://darwin.cwru.edu/despair/

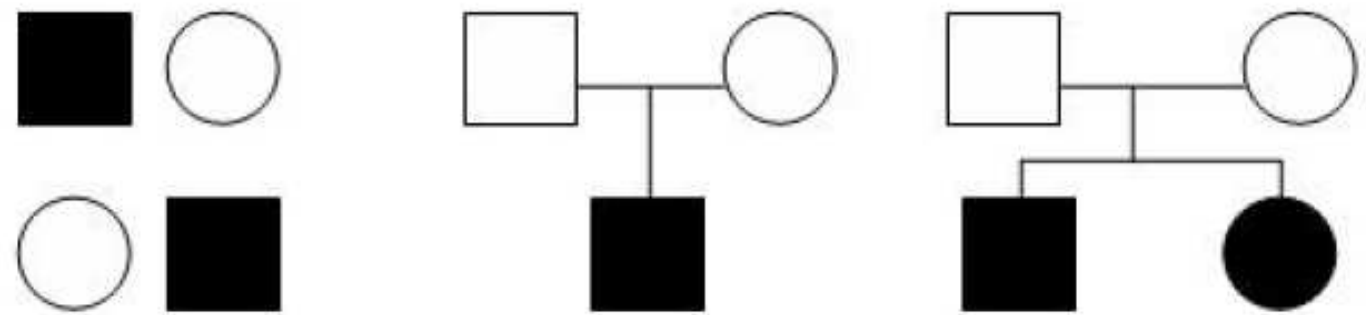
Association study

- There are a number of R packages which provide functions for association design involving both population-based and family-based designs.
- In particular, power.casectrl in **genetics** is appropriate for case-control design under a range of genetic models. Function pbsize in gap is appropriate when a whole population is considered. Function ntdt in **powerpkg** provides number of trios required for TDT. Functions haplo.power.cc and haplo.power.qt from **haplo.stats** are designed for haplotype analyses of binary and continuous traits.
- However, we here only focus on designs as in the current context of GWAS.

Niel Risch



Designs for GWAS



Three common genetic association designs involving unrelated individuals (left), nuclear families with affected singletons (middle) and affected sib-pairs (right). Males and females are denoted by squares and circles with affected individuals filled with black and unaffected individuals being empty.

The disease model

- Allele A, a with population frequencies p, q=1-p, A=disease allele
- The penetrances with 0,1,2 copies of for are f0,f1,f2
- Assuming Hardy-Weinberg equilibrium, the population prevalence is

$$K = p^2 f^2 + 2pq f_1 + q^2 f_0$$

- For a multiplicative model of genotypic relative risk (GRR)

$$K = p^2\gamma^2 + 2pq\gamma + q^2 = (p\gamma + q)^2$$

- The offspring, sibling relative risks are

$$\lambda_O = 1+w \text{ and } \lambda_S = (1+1/2w)^2, w = (pq(\gamma-1)^2)/(p\gamma+q)^2$$

The normal approximation

- Assuming B_i, i=1,…, N are i.i.d. random variable with mean and variance being 0, 1 under the null hypothesis, μ and σ^2 under the alternative hypothesis, then the statistic

$$\sum_{i=1}^{N} B_i/N$$

- has mean 0 and variance under the null but mean $\sqrt{N\mu}$ and σ^2 under the alternative.
- The sample size N for a given significance level α and power 1-β can be estimated by

$$(Z_\alpha - \sigma Z_{1-\beta})^2/\mu^2$$

- In the context of GWAS we can assume $\alpha=5 \times 10^{-8}$ and β=0.2, respectively.

Family data

- In the case of affected sib pairs, alleles shared and nonshared as Bi and scoring 1 and -1. They have value 0.5 under the null and 2Y-1, 4Y(1-Y) under the alternative, where Y=(1+w)/(2+w).
- In the case TDT, the probabilities of a parent of an affected child being heterozygous (h) for singletons and sib pairs are given by

$$pq(\gamma+1)/(p\gamma+q) \text{ and } pq(\gamma+1)^2/[2(\gamma p+q)^2+pq(\gamma-1)^2]$$

- The score for transmission is 1/sqrt(h), 0, -1/sqrt(h) and we have Bi has mean and variance 0, 1 under the null and

$$\sqrt{h}(\gamma-1)/(\gamma+1) \text{ and } 1-h[(\gamma-1)/(\gamma+1)]^2$$

- under the alternative
- See fbsize function in R/gap

Family designs

		Linkage			Association					
γ	p	Y	N_L	P_A	H_1	N_{tdt}	H_2	$N_{asp/tdt}$	λ_o	λ_s
4.00	0.01	0.520	6400	0.800	0.048	1098	0.112	235	1.08	1.09
	0.10	0.597	277	0.800	0.346	151	0.537	48	1.48	1.54
	0.50	0.576	445	0.800	0.500	104	0.424	62	1.36	1.39
	0.80	0.529	3023	0.800	0.235	223	0.163	162	1.12	1.13
2.00	0.01	0.502	445839	0.667	0.029	5824	0.043	1970	1.01	1.01
	0.10	0.518	8085	0.667	0.245	696	0.323	265	1.07	1.08
	0.50	0.526	3752	0.667	0.500	340	0.474	180	1.11	1.11
	0.80	0.512	17904	0.667	0.267	640	0.217	394	1.05	1.05
1.50	0.01	0.501	6942837	0.600	0.025	19321	0.031	7777	1.00	1.00
	0.10	0.505	101898	0.600	0.214	2219	0.253	941	1.02	1.02
	0.50	0.510	27041	0.600	0.500	950	0.490	485	1.04	1.04
	0.80	0.505	101898	0.600	0.286	1663	0.253	941	1.02	1.02

Y=probability of allele sharing; P_A=probability of transmitting disease allele A; H_1, H_2=proportions of heterozygous parents

Expected frequencies for case-control design

- This can be tabulated as follows,

	Affected genotype	Nonaffected genotype	
A	$\pi\gamma^2 p^2 + \pi\gamma pq$	$(1-\pi\gamma^2)p^2 + (1-\pi\gamma)pq$	p
a	$\pi\gamma pq + \pi q^2$	$(1-\pi\gamma)pq + (1-\pi)q^2$	q
	$\pi(\gamma p + q)^2$	$1 - \pi(\gamma p + q)^2$	1

- and can be referred to a chi-squared distribution with one degree of freedom

- See pbsize function in R/gap.

Case-control design

		K			
γ	p	1%	5%	10%	20%
4.0	0.01	46638	8951	4240	1885
	0.10	8173	1569	743	331
	0.50	10881	2089	990	440
	0.80	31444	6035	2859	1271
2.0	0.01	403594	77458	36691	16307
	0.10	52660	10107	4788	2128
	0.50	35252	6766	3205	1425
	0.80	79317	15223	7211	3205
1.5	0.01	1598430	306770	145312	64583
	0.10	191926	36835	17448	7755
	0.50	97922	18793	8902	3957
	0.80	191926	36835	17448	7755

A summary of designs

- These calculation disregards linkage disequilibrium.
- For family data, association is more powerful than linkage.
- Population-based study can be more powerful than family-based study.

A variation: case-cohort design

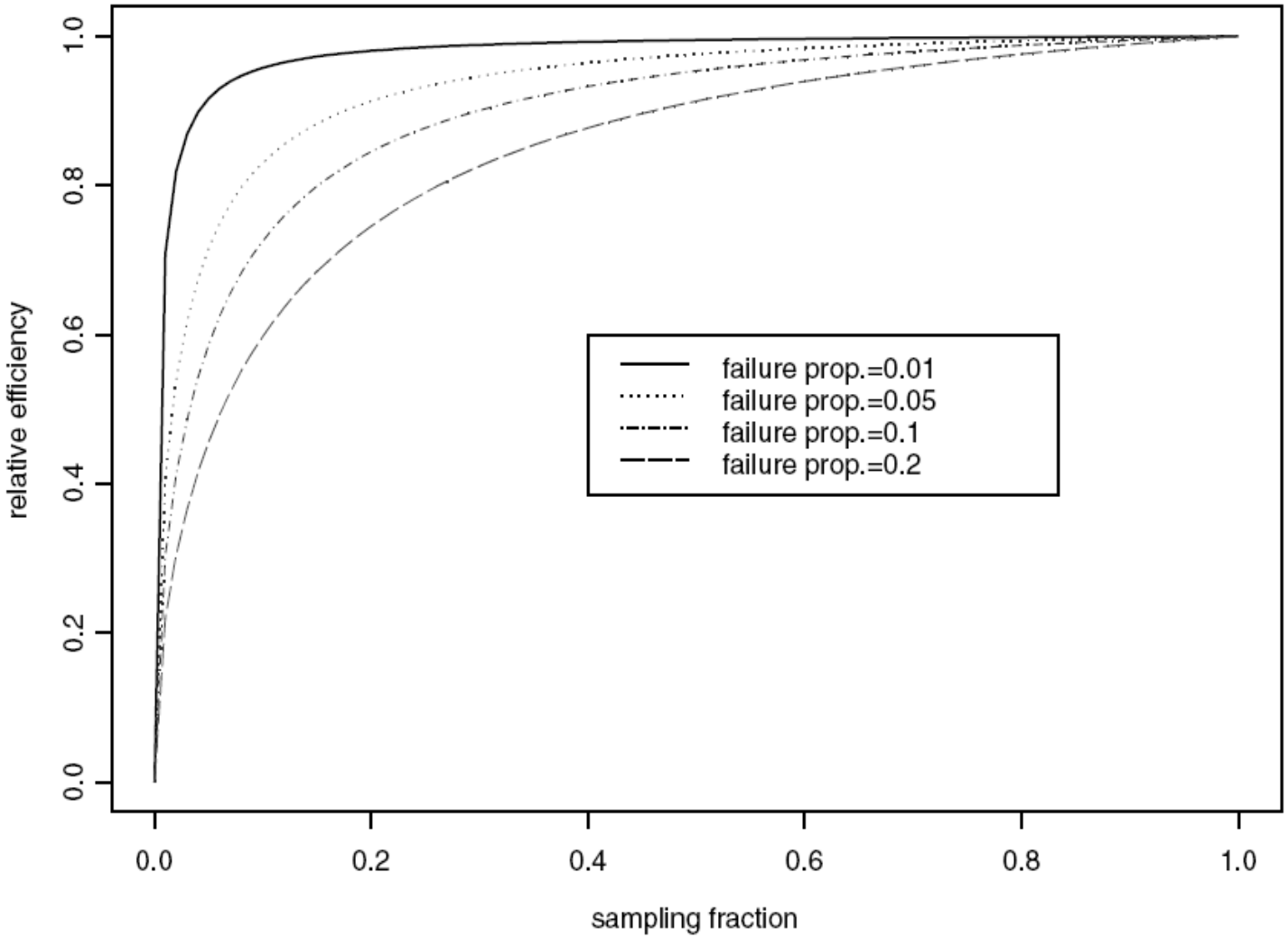
- Assumption: the censoring distributions in two groups, small but moderate number of failures in the full cohort and no ties.
- The power can be obtained from the following expression,

$$\Phi(Z_\alpha + m^{0.5}\theta\sqrt{p_1 p_2 p_D/q + (1-q)p_D})$$

- where α is the significance level, θ is the log-hazard ratio for two groups, p_j, j=1,2 are the proportion of the two groups in the population, m is the total number subjects in the subcohort, p_D is the proportion of the failures in the full cohort, q is the sampling fraction of the subcohort.
- Alternatively, sample size can be obtained (n is the size of cohort),

$$m = nBp_D/(n - B(1-p_D)) \quad B = (Z_{1-\alpha} + Z_\beta)^2/(\theta^2 p_1 p_2 p_D))$$

Relative efficiency of the case-cohort design compared to the full cohort



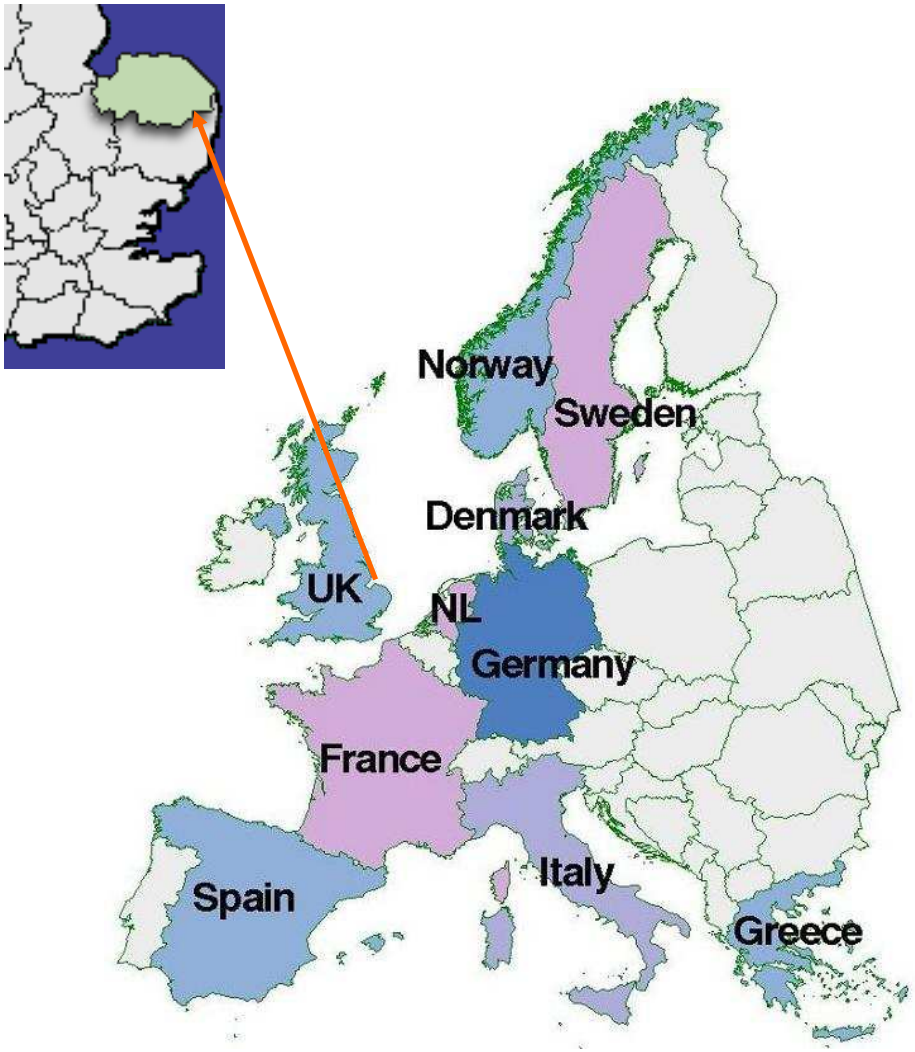
A summary of designs

The European Prospective Investigation into Cancer and Nutrition (EPIC) is coordinated by Dr Elio Riboli, Head of the Division of Epidemiology, Public Health and Primary Care at the Imperial College London.

EPIC was designed to investigate the relationships between diet, nutritional status, lifestyle and environmental factors and the incidence of cancer and other chronic diseases. EPIC is the largest study of diet and health ever undertaken, having recruited over half a million (520,000) people in ten European countries: Denmark, France, Germany, Greece, Italy, The Netherlands, Norway, Spain, Sweden and the United Kingdom.

The EPIC-Norfolk study

EPIC-Norfolk participants are men and women (based on over 30,000 people) who were aged between 45 and 74 when they joined the study, who lived in Norwich and the surrounding towns and rural areas. They have been contributing information about their diet, lifestyle and health through questionnaires, and through health checks carried out by EPIC nurses.



The case-cohort design for EPIC-Norfolk

- It originally followed case-control design (e.g., WTCCC with seven cases and common controls) with 3425 cases and 3400 controls.
  - It is potentially more powerful.
  - Controls are selected.
- It has then been changed into case-cohort design, in which cases are defined to be individuals whose BMI above 30 and controls are a random sample (subcohort) of the EPIC-Norfolk cohort which includes obese individuals.
  - The subcohort is representative of the whole population and allows for a range of traits to be examined.
  - The analysis is potentially more involved but established.

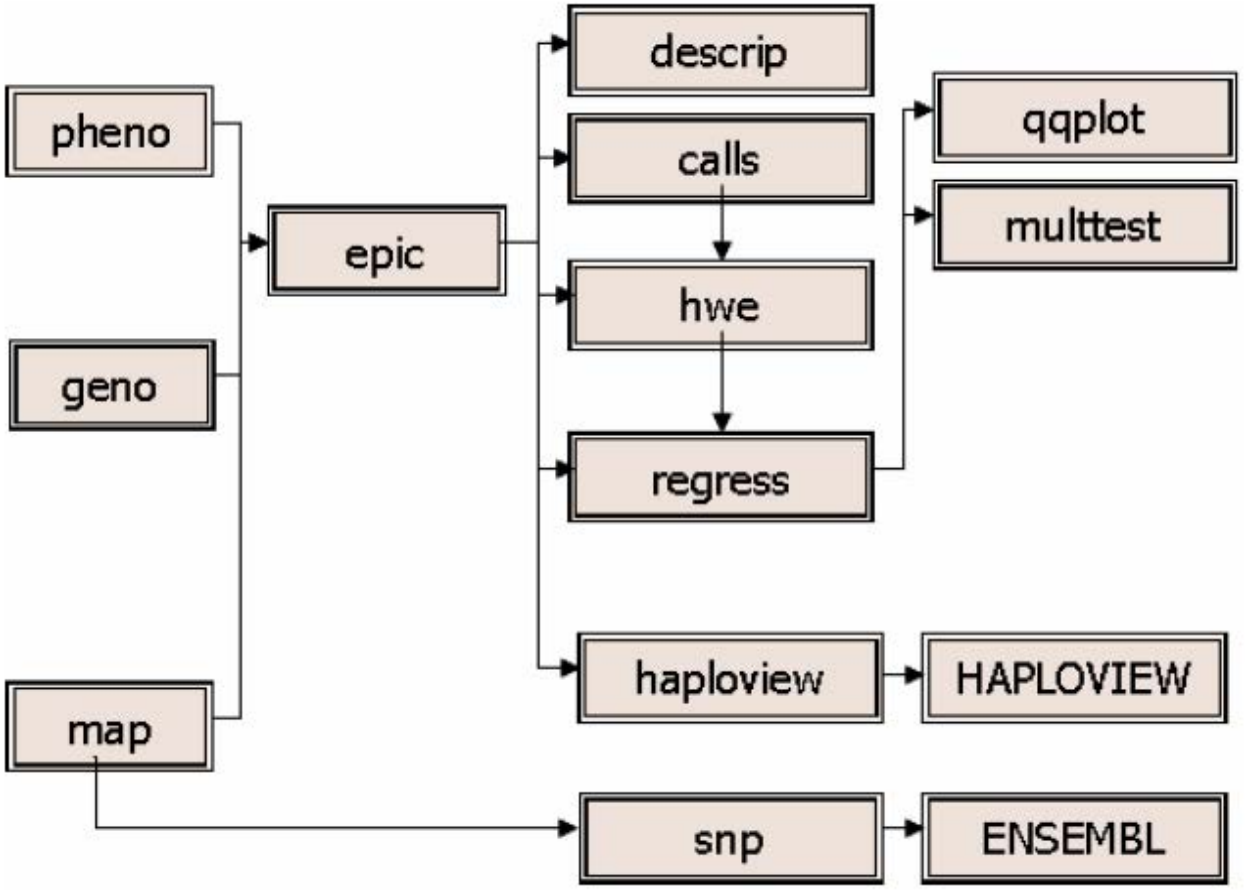
Power and sample size

- It started with assessment of how the power is compromised relative to the original case-control design.
- This was followed by power/sample size calculation using methods established by Cai and Zeng (2004) as implemented in an R function, noting a number of assumptions.
- More practically, it was also envisaged that a proper representative sample of a total of 25,000 individuals would be 10%; the subcohort is then approximately 2,500.
- The total sample was split between two stages.
- Affymetrix 500K data were available for 3850 individuals
- Illumina 317K -- it came at a later time and the quality of data appears to be poor?
- The focus has therefore been Affy500K, but with a possible comeback.

Analysis

- An incremental approach was adopted since the storage and computing power were somewhat uncertain.
- This was predated with controls from the breast cancer study, involving about 400 individuals with Perlegen 250K GeneChips.
- QC including call rates and HWE was feasible with SAS/Genetics (~30GB) which provides a good estimate of the storage for all individuals (~380GB).
- The Linux platform seemed to be favourable.

EPIC400 analysis



A flowchart of the EPIC 400 analysis, with modules in brackets

The analysis for GWAS

- QC including visualisation of clustering, outliers, was largely done by colleagues at Sanger (as for WTCCC)
- The overall strategy was data partition, i.e., by chromosome and further by region (30) in each chromosome, largely on a long, skinny data format
- A major advantage is that the analysis can be resumed whenever the system experiences problems
- We stuck to SAS to allow for reliability and flexibility with or without SAS/Genetics, for BMI/obesity as continuous and binary outcomes are readily tackled with REG/LOGISTIC procedures – most outputs are available from the output delivery system (ODS)
- The picture was eventually changed with a revised coding algorithm and the use of imputed data

Additional analysis

- Population stratification via EIGENSTRAT
  - SAS is very handy since a single put statement is sufficient to generate the output.
- Collaborative (e.g. height) and consortium work (GIANT)
  - On the UK side, this is mainly involved with IMPUTE/SNPTEST, with inputs on strand, standard error, quantitative traits, outputs.
  - This facilitates meta-analysis considerably.

LDL

LDL-cholesterol concentrations: a genome-wide association study

Manjinder S Sandhu, Dawn M Waterworth*, Sally L Debenham*, Eleanor Wheeler, Konstantinos Papadakis, Jing Hua Zhao, Kijoung Song, Xin Yuan, Toby Johnson, Sofie Ashford, Michael Inouye, Robert Luben, Matthew Sims, David Hadley, Wendy McArdle, Philip Barter, Y Antero Kesäniemi, Robert W Mahley, Ruth McPherson, Scott M Grundy, Wellcome Trust Case Control Consortium†, Sheila A Bingham, Kay-Tee Khaw, Ruth J F Loos, Gérard Waeber, Inês Barroso, David P Strachan, Panagiotis Deloukas, Peter Vollenweider, Nicholas J Wareham, Vincent Mooser*

BMI/obesity

Common variants near *MC4R* are associated with fat mass, weight and risk of obesity

Ruth J F Loos[*,1,2,73], Cecilia M Lindgren[3,4,73], Shengxu Li[1,2,73], Eleanor Wheeler[5], Jing Hua Zhao[1,2], Inga Prokopenko[3,4], Michael Inouye[5], Rachel M Freathy[6,7], Antony P Attwood[5,8], Jacques S Beckmann[9,10], Sonja I Berndt[11], The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial[71], Sven Bergmann[9,12], Amanda J Bennett[3,4], Sheila A Bingham[13], Murielle Bochud[14], Morris Brown[15], Stéphane Cauchi[16], John M Connell[17], Cyrus Cooper[18], George Davey Smith[19], Ian Day[18], Christian Dina[16], Subhajyoti De[20], Emmanouil T Dermitzakis[5], Alex S F Doney[21], Katherine S Elliott[3], Paul Elliott[22,23], David M Evans[3,19], I Sadaf Farooqi[2,24], Philippe Froguel[16,25], Jilur Ghori[5], Christopher J Groves[3,4], Rhian Gwilliam[5], David Hadley[26], Alistair S Hall[27], Andrew T Hattersley[6,7], Johannes Hebebrand[28], Iris M Heid[29,30], KORA[71], Blanca Herrera[3,4], Anke Hinney[28], Sarah E Hunt[5], Marjo-Riitta Jarvelin[22,23,31], Toby Johnson[9,12,14], Jennifer D M Jolley[8], Fredrik Karpe[4], Andrew Keniry[5], Kay-Tee Khaw[32], Robert N Luben[32], Massimo Mangino[33], Jonathan Marchini[34], Wendy L McArdle[35], Ralph McGinnis[5], David Meyre[16], Patricia B Munroe[36], Andrew D Morris[21], Andrew R Ness[37], Matthew J Neville[4], Alexandra C Nica[5], Ken K Ong[1,2], Stephen O'Rahilly[2,24], Katharine R Owen[4], Colin N A Palmer[38], Konstantinos Papadakis[26], Simon Potter[5], Anneli Pouta[31,39], Lu Qi[40], Nurses' Health Study[71], Joshua C Randall[3,4], Nigel W Rayner[3,4], Susan M Ring[35], Manjinder S Sandhu[1,32], André Scherag[41], Matthew A Sims[1,2], Kijoung Song[42], Nicole Soranzo[5], Elizabeth K Speliotes[43,44], Diabetes Genetics Initiative[71], Holly E Syddall[18], Sarah A Teichmann[20], Nicholas J Timpson[3,19], Jonathan H Tobias[45], Manuela Uda[46], The SardiNIA Study[71], Carla I Ganz Vogel[28], Chris Wallace[36], Dawn M Waterworth[42], Michael N Weedon[6,7], The Wellcome Trust Case Control Consortium[72], Cristen J Willer[47], FUSION[71], Vicki L Wraight[2,24], Xin Yuan[42], Eleftheria Zeggini[3], Joel N Hirschhorn[44,48–51], David P Strachan[26], Willem H Ouwehand[8], Mark J Caulfield[36], Nilesh J Samani[33], Timothy M Frayling[6,7], Peter Vollenweider[52], Gerard Waeber[52], Vincent Mooser[42], Panos Deloukas[5], Mark I McCarthy[3,4,73], Nicholas J Wareham[1,2,73] & Inês Barroso[5,73]

Height

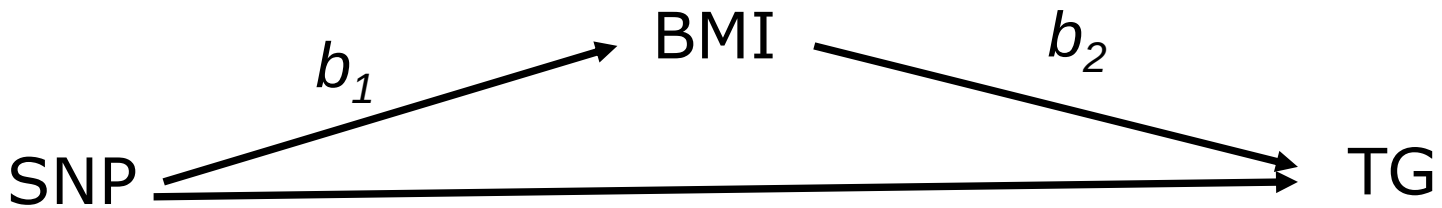
Genome-wide association analysis identifies 20 loci that influence adult height

Michael N Weedon[1,2,23], Hana Lango[1,2,23], Cecilia M Lindgren[3,4], Chris Wallace[5], David M Evans[6], Massimo Mangino[7], Rachel M Freathy[1,2], John R B Perry[1,2], Suzanne Stevens[7], Alistair S Hall[8], Nilesh J Samani[7], Beverly Shields[2], Inga Prokopenko[3,4], Martin Farrall[9], Anna Dominiczak[10], Diabetes Genetics Initiative[21], The Wellcome Trust Case Control Consortium[21], Toby Johnson[11–13], Sven Bergmann[11,12], Jacques S Beckmann[11,14], Peter Vollenweider[15], Dawn M Waterworth[16], Vincent Mooser[16], Colin N A Palmer[17], Andrew D Morris[18], Willem H Ouwehand[19,20], Cambridge GEM Consortium[22], Mark Caulfield[5], Patricia B Munroe[5], Andrew T Hattersley[1,2], Mark I McCarthy[3,4] & Timothy M Frayling[1,2]

Adult height is a model polygenic trait, but there has been limited success in identifying the genes underlying its normal variation. To identify genetic variants influencing adult human height, we used genome-wide association data from 13,665 individuals and genotyped 39 variants in an additional 16,482 samples. We identified 20 variants associated with adult height ($P < 5 \times 10^{-7}$, with 10 reaching $P < 1 \times 10^{-10}$). Combined, the 20 SNPs explain ~3% of height variation, with a ~5 cm difference between the 6.2% of people with 17 or fewer 'tall' alleles compared to the 5.5% with 27 or more 'tall' alleles. The loci we identified implicate genes in Hedgehog signaling (*IHH, HHIP, PTCH1*), extracellular matrix (*EFEMP1, ADAMTSL3, ACAN*) and cancer (*CDK6, HMGA2, DLEU7*) pathways, and provide new insights into human growth and developmental processes. Finally, our results provide insights into the genetic architecture of a classic quantitative trait.

Specific analysis

- Which trait MC4R has effect on?
- Interpretation of mediation
  - Path analysis – shows mainly on BMI and not others
  - Error propagation as appropriate for meta-analysis



As is the case with FTO and T2D, the indirect effect (IE) from MC4R SNP to TG via BMI is $b_1 b_2$, with $SE(IE) \approx b_1 SE(b_2)$

Reflection on the study design

	Study 1 (EPIC-Norfolk subcohort) n=2269		Study 2 (EPIC-Norfolk obese set) n=1009		Study 3 (1958 British birth cohort) n=1375		Study 4 (CoLaus) n=5367		Study 5 (GEMS study) n=1665	
	β coeff (SE)	p value	β coeff (SE)	p value	β coeff (SE)	p value	β coeff (SE)	p value	β coeff (SE)	p value
rs4420638	0·24 (0·04)	$1·9\times10^{-9}$	0·14 (0·06)	0·02	0·25 (0·04)	$2·8\times10^{-9}$	0·05 (0·01)	$6·2\times10^{-12}$	0·04 (0·01)	$5·6\times10^{-3}$
rs599839	−0·15 (0·04)	$5·8\times10^{-5}$	−0·23 (0·06)	$7·6\times10^{-5}$	−0·14 (0·04)	$4·3\times10^{-4}$	−0·04 (0·01)	$1·6\times10^{-7}$	−0·06 (0·01)	$2·0\times10^{-5}$
rs4970834	−0·13 (0·04)	$1·1\times10^{-3}$	−0·18 (0·06)	$5·5\times10^{-3}$	−0·11 (0·04)	0·01	−0·04 (0·01)	$1·9\times10^{-6}$	−0·04 (0·01)	$2·8\times10^{-3}$
rs562338	−0·17 (0·04)	$6·0\times10^{-6}$	−0·11 (0·06)	0·07	−0·18 (0·05)	$1·1\times10^{-4}$	−0·03 (0·01)	$2·7\times10^{-6}$	−0·02 (0·01)	0·18
rs7575840	0·15 (0·03)	$6·3\times10^{-6}$	0·15 (0·05)	$2·4\times10^{-3}$	0·04 (0·04)	0·26	0·03 (0·01)	$1·9\times10^{-6}$	0·02 (0·01)	0·13
rs478442	−0·16 (0·04)	$2·1\times10^{-5}$	−0·07 (0·06)	0·25	−0·16 (0·04)	$3·6\times10^{-4}$	−0·03 (0·01)	$2·7\times10^{-5}$	−0·02 (0·01)	0·06
rs4591370	−0·17 (0·04)	$7·7\times10^{-6}$	−0·06 (0·06)	0·28	−0·16 (0·04)	$4·2\times10^{-4}$	−0·03 (0·01)	$3·2\times10^{-5}$	−0·02 (0·01)	0·06
rs4560142	−0·16 (0·04)	$1·6\times10^{-5}$	−0·06 (0·06)	0·27	−0·16 (0·04)	$4·2\times10^{-4}$	−0·03 (0·01)	$3·5\times10^{-5}$	−0·03 (0·01)	0·05
rs576203	−0·16 (0·04)	$1·2\times10^{-5}$	−0·07 (0·06)	0·25	−0·16 (0·04)	$3·5\times10^{-4}$	−0·03 (0·01)	$3·5\times10^{-5}$	−0·02 (0·01)	0·06
rs506585	−0·16 (0·04)	$1·7\times10^{-5}$	−0·06 (0·06)	0·31	−0·16 (0·04)	$3·5\times10^{-4}$	−0·03 (0·01)	$4·2\times10^{-5}$	−0·03 (0·01)	0·05
rs488507	−0·14 (0·04)	$1·3\times10^{-4}$	−0·07 (0·06)	0·25	−0·16 (0·04)	$3·3\times10^{-4}$	−0·03 (0·01)	$3·4\times10^{-5}$	−0·02 (0·01)	0·07
rs538928	−0·16 (0·04)	$5·0\times10^{-5}$	−0·01 (0·06)	0·92	−0·16 (0·04)	$3·5\times10^{-4}$	−0·03 (0·01)	$3·6\times10^{-5}$	−0·02 (0·01)	0·05
rs10402271	0·04 (0·03)	0·17	0·11 (0·05)	0·02	0·12 (0·04)	$7·5\times10^{-4}$	0·02 (0·01)	$5·2\times10^{-4}$	0·04 (0·01)	$8·3\times10^{-4}$
rs693	−0·12 (0·03)	$1·3\times10^{-4}$	−0·07 (0·05)	0·15	−0·06 (0·03)	0·06	−0·03 (0·01)	$1·0\times10^{-5}$	−0·02 (0·01)	0·16

Webtable 3: Associations between Affymetrix SNPs with a combined p value of $<1·0\times10^{-7}$ and circulating concentrations of LDL cholesterol in independent study populations

Our best practice

- Linux clusters are now ready for comphensive analyses.
- Linux/awk script is light and appears to be more transparent than Perl, Java which is more professional.
- awk proves very useful and can be transformed to Perl. In fact, any statistical package which processes data elements would be less efficient. An example is the transformation of long, wide, transposed format noted earlier.
- They call C/C++ programs such as IMPUTE/SNPTEST.
- SAS is still useful for data preparation, and in a sense less professional than DBMS such as Oracle but enjoys a large user community and has facility for data analysis.
- SAS 9.2 PROTO procedure is yet to be explored.

Haplotype analysis

```
%macro wreg(no,model);
proc surveyreg;
        ods output parameterestimates=bmi&no
                        (where=(parameter^="Intercept"));
        cluster id;
        &model / clparm;
        weight p;
run;
data bmi&no;
        model=&no;
        set bmi&no;
run;
%mend wreg;
%wreg(1,model lbmi1=sex age1 h1--h5);
%wreg(2,model lbmi2=sex age2 h1--h5);
```

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